ORIGINAL ARTICLE

Comparative study of enema retention and preference in ulcerative colitis

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Background: Therapeutic enemas are often used to treat active colitis but their retention may be limited because of urgency to defecate. Some preparations may be better retained and tolerated than others because of their physical properties.
Aim: To compare patient preference and retention of four therapeutic enemas, including a nicotine enema, in patients with ulcerative colitis (UC).
Methods: Twenty four patients with active UC received the four trial enemas—corticosteroid, 5-amino salicylate (5-ASA), and nicotine liquid enemas and a corticosteroid foam, in a randomised order, taking one enema on each of four successive nights. Patients scored them 1 to 4 for ease of administration and retention, degree of abdominal bloating, and for their overall preference.
Results: Fifteen patients rated nicotine their overall favourite or second favourite, compared with 14 for corticosteroid foam and 11 for 5-ASA and corticosteroid liquids, but this was not significant ($p = 0.302$). Overall, there was no significant difference in overnight retention. However, the nicotine enema tended to be less well retained in patients with milder urgency but a higher proportion retained it overnight with more severe urgency ($p = 0.031$ compared with 5-ASA enema).
Conclusion: There was no significant difference in patient preference or overall duration of retention for the four enemas.

While therapeutic enemas are useful in the management of patients with inflammatory bowel disease[1–6] poor retention can limit their effect, particularly in patients with active disease associated with urgency of defecation. Enemas may be retained for only short periods, and in some cases much of the enema may be passed soon after administration. Fear of incontinence while in bed is also a problem.

During a study of liquid nicotine enemas as treatment for ulcerative colitis (UC),[7] some patients commented on how readily it was retained—and without discomfort. To examine the hypothesis that nicotine enemas may be better retained, we compared the retention of nicotine enemas with three others, all conventionally used in the treatment of colitis—two of them liquid enemas and one foam enema. The aim of the study was limited to identification of the patients' preference for each enema and duration of retention in subjects with active UC—efficacy was not considered. In doing so we used a novel design in which patient preference was based on exposure to each enema, once only on consecutive nights—a design that breaks with traditional comparisons in which efficacy is an issue.

METHODS

Subjects

A total of 40 consecutive patients, attending the colitis clinic, who fulfilled diagnostic criteria for UC with active symptoms, were reviewed and considered for the study. Twenty four of these patients who required topical treatment were recruited to the study. The principal reasons for patients not participating were unsuitability for topical treatment or patients declining to take part. The severity of disease on entry to the trial was assessed according to a composite scoring system based on the ulcerative colitis disease Activity Index (UCDAI)[2] (see box). This composite score was derived from symptoms only; it included stool frequency and consistency, urgency to defecate, and the presence of blood in the stool—these are often perceived by patients to be the most troublesome symptoms. Sigmoidoscopy was not performed as the purpose of the score was simply to ensure that all patients had symptomatically active disease on entry to the study. All gave written informed consent before participation in the study, which was approved by the South East Wales Local Research Ethics Committee. Subjects were excluded if they were known to be intolerant of any of the trial medication, and those who might have been pregnant or were lactating.

Trial enemas

Three liquid preparations, each about 100 ml in volume, were packaged in identical soft low density polyethylene bottles (Forrest Labs, Bexley, UK), together with one foam enema; their compositions are below:

(1) The prednisolone sodium phosphate liquid enema (Predsol, Celltech) was an aqueous formulation with a viscosity of 0.39 mPas, containing 20 mg of prednisolone as the sodium phosphate ester in a buffered solution. Included in the formulation are methyl, ethyl, propyl, and butyl 4-hydroxybenzoates as preservatives, disodium edentate as a chelating agent, sodium acid phosphate and disodium hydrogen phosphate as buffering agents, and sodium hydroxide to adjust its pH to 6.3.

(2) The 5-amino salicylate (5-ASA) liquid enema (Pentasa, Ferring Pharma) was an aqueous suspension, pH 4.6 and viscosity 0.49 mPas, containing 1 g of mesalazine in distilled water. It also contains sodium metabisulphite as an antioxidant.

(3) The nicotine liquid enema (SLA Pharma, Watford, UK) was an aqueous formulation that contained 6 mg of nicotine base (Seigfried Labs, Zofingen, Switzerland)

Abbreviations: UC, ulcerative colitis; AE, adverse event; UCDAI, ulcerative colitis disease activity index; 5-ASA, 5-amino salicylate

Composite score of disease activity

Stool frequency
- 0; usual number of stools for this patient
- 1; 1–2 stools per day more than usual
- 2; 3–4 stools per day more than usual
- 3; at least 5 stools per day more than usual

Stool consistency
- 0; formed
- 1; loose
- 2; watery

Urgency of defecation,
- 0; none
- 1; mild
- 2; moderate
- 3; severe (including incontinence)

Rectal bleeding
- 0; none
- 1; streaks of blood with stools less than half the time
- 2; obvious blood with stools most of the time
- 3; blood alone passed

Maximum total score = 11
Adapted from Sutherland *et al*.[2]

complexed to 400 mg of carbomer powder (Carbopol 974P, Noveon, Cleveland, OH).[8] The addition of 100 mg of xanthan gum (Keltrol, Kelco) made the enema thixotropic and increased its viscosity. Trometamol, TRIS, (S Banner and Son, UK), served as a buffer to produce a solution of pH 5.2 with a viscosity of 172 mPas.[9 10]

(4) The Predfoam enema (Pharmax) was a white mucoadherent aerosol foam, with a dynamic viscosity of 5.7 mPas and pH of 4.8, which contained prednisolone metasulphobenzoate sodium, equivalent to 20 mg of prednisolone per metered dose of about 50 ml. The product also contained disodium edentate as a chelating agent, phenoxyethanol and sorbic acid as preservatives, and propellant gases.

''Latin square'' study design and sample size

Patients who required or were already taking topical treatment for their colitis were given the four trial enemas in a randomised order, taking one enema on each of four successive nights. A washout period between enemas was not included as this would have introduced a time delay between enemas, allowing changes in disease severity to affect the results. Twenty four subjects were entered into a Latin square design in which all permutations of the order of enema administration were included once only; this ensured that any carryover effect of earlier enemas affecting subsequent ones, either by clinical improvement or rectal irritation, did not affect the overall results.

The comparatively modest sample size of 24 was calculated to have sufficient power to meet the aims of the study because of its design. A four way crossover study in which each subject is used four times, by exposure to all four treatments, is at least as powerful as a parallel groups study with four times the number of patients—96 in this case. The power may actually be greater than for 96 different patients receiving only one treatment as a subject's responses to different, comparable treatments usually produces positive correlation when they rank the treatments in order of preference.

Table 1 Demographic details of subjects

Sex	
M/F	13/11
Age, years	
Mean/range	45.1/19–84
Extent of colitis	
Rectal	6
Rectosigmoid	7
Left sided	6
Total	4
Unknown	1
Previous enema use	
Yes/no	23/1
Current topical treatment on trial entry	
None	15
Foam	5
Liquid	3
Suppository	1
Concomitant oral drugs	
5-ASA	14
Prednisolone	6
Thiopurines	6
Smoking status	
Non/former	11/13

Subjects were advised to administer enemas slowly and in a consistent way—lying on their side in the left lateral decubitus position, after first warming the enema to body temperature. They were asked to record their preferences for each enema on a diary card and were interviewed either in clinic or by telephone after one week.

Evaluation procedures

In each case, patients were asked whether the enema was initially retained and then whether it was retained overnight—defined as at least eight hours; if less than the whole night, the duration of enema retention was recorded. They also recorded any associated adverse events (AEs). Patients ranked each of the four enemas, scoring them 1 to 4 for ease of administration, ease of retention both initially and overnight, degree of any abdominal bloating, and for their overall preference.

Statistical analysis

Preference scores were compared between enemas using three way analysis of variance modelling by subject, period, and enema. Proportions with initial retention were compared between groups by the χ^2 test. Proportions achieving full overnight retention were compared by the McNemar test, taking the mid-p two tailed p value and setting significance at the conventional 5% level. A sub-analysis of the effect of urgency on overnight retention was performed and the results interpreted cautiously.

RESULTS

All 24 subjects recruited, 13 male, with a mean age of 45 years, completed the study. Eleven were non-smokers and 13 former smokers; table 1 gives demographic details of the patients. Table 2 shows the disease activity of the patient cohort on entry to the study. The mean score of disease activity was 5.6 with a range of 1 to 11—the maximum score possible with this index. It is possible to have active disease with a score of only 1, as it is a system based on the patient's observations of a change in bowel habit from their normal. A

Table 2 Disease activity on trial entry

	Symptom			
Activity score	Frequency	Consistency	Urgency	Bleeding
0	5	6	4	4
1	7	12	6	9
2	4	6	9	9
3	8	–	5	2

The number of patients giving each score for each particular symptom.

minor protocol deviation occurred in two patients who took the enemas in the wrong order on two occasions. However, analysis by three way analysis of variance adjusts effectively for this.

The trial enemas were retained initially in 21, 19, 22, and 21 patients for Predsol, Pentasa, Predfoam, and nicotine respectively; this was not significant ($\chi^2 = 1.69$, df = 3, p = 0.64). Overnight leakage occurred more often with the predsol enema—four patients.

Table 3 shows overnight retention, including a sub-analysis of the effect of urgency. For all 24 patients, there was no significant difference in complete overnight retention (p = 0.75, 0.75 and 0.73 for Predsol, Pentasa, and Predfoam respectively when compared with the nicotine enema). Retention was reduced in patients with more severe urgency—78% of enemas were retained overnight for mild or no urgency, compared with 57% for moderate or severe urgency. The nicotine enema was less well retained than the others for milder urgency, but significance was not quite reached (p = 0.125, 0.063, and 0.063 for Predsol, Pentasa, and Predfoam when compared with the nicotine enema). However, in patients with more severe urgency, nicotine was better retained than the others, reaching significance in the comparison with Pentasa (p = 0.125, 0.031, and 0.125 for Predsol, Pentasa, and Predfaom when compared with the nicotine enema).

Overall, nicotine, and Predfoam were the most preferred enemas (table 4). Fifteen subjects rated nicotine as their favourite or second favourite for overall preference, compared with 14 for Predfoam and 11 for Predsol and Pentasa; however the differences did not reach significance (p = 0.73, one way anlysis of variance). Predfoam was rated easiest to administer by 12 patients, compared with five, six, and seven patients for Predsol, Pentasa, and nicotine respectively. However, it was also most likely to be rated least favourite by patients—this polarisation of patients' views was present in all categories for Predfoam but not for the other enemas examined. Of the five patients taking a foam enema on entry to the study, two most preferred Predfoam while three preferred liquid enemas; of the three patients previously using a liquid enema, two preferred Predfoam while one preferred a liquid enema.

The highest incidence of AEs was associated with Predsol—six AEs, compared with three, one, and none with nicotine, Predfoam, and Pentasa respectively. These AEs were either headache, nausea, or disturbed sleep and were graded as mild or moderate in magnitude.

DISCUSSION

There was no significant difference in patient preference for the four enemas or in overnight retention for all 24 patients. However, the nicotine enema tended to be less well retained in patients with milder urgency to defecate but retained for longer in those with more severe urgency (p = 0.031 compared with Pentasa). The patients' view of Predfoam tended to be polarised with nine rating it their most preferred enema and eight as the least preferred. In the eight patients already using an enema on entry to the study, their preference was unrelated to the enema they had been using.

Although 24 patients was a comparatively small number, the four way crossover design gives a power equivalent to a parallel groups study of 96 patients and, as patients scored each of the four treatments, positive correlation gave additional power. The results of the sub-analysis concerning urgency are less robust as smaller patient numbers are involved. The three liquid enemas were all colourless and contained in identical bottles to ensure double blinding; only investigator blinding was possible for the foam enema. The four enemas were taken on successive nights without a washout period to minimise any change in the patients' disease activity during the study. Any carryover from one enema to the next, because of irritation or other effects on the rectal mucosa, was countered by including all permutations

Table 3 Overnight retention: the effect of urgency

Urgency	Enema	Number retained overnight	Mid p value compared with nicotine	Difference in proportion retained compared with nicotine	95% Confidence intervals
All—24 patients	Predsol	15 (6.0)	0.75	+0.04	−0.20 to +0.28
	Pentasa	15 (5.8)	0.75	+0.04	−0.20 to +0.28
	Predfoam	17 (6.7)	0.73	−0.04	−0.26 to +0.18
	Nicotine	16 (5.5)			
None/mild—10 patients	Predsol	8 (6.6)	0.125	−0.30	−0.57 to +0.05
	Pentasa	9 (7.2)	0.063	−0.40	−0.68 to +0.002
	Predfoam	9 (7.3)	0.063	−0.40	−0.68 to +0.002
	Nicotine	5 (4.3)			
Moderate/severe—14 patients	Predsol	7 (5.6)	0.125	+0.29	−0.06 to +0.56
	Pentasa	6 (4.8)	0.031*	+0.36	+0.05 to +0.58
	Predfoam	8 (6.2)	0.125	+0.21	−0.04 to +0.44
	Nicotine	11 (6.4)			

The number of patients who, for each enema, were able to retain it overnight—for eight hours. The mean duration of retention in hours is given in parentheses. Mid-p two tailed p values for the McNemar test compare the nicotine enema with each of the others. Overall results and a sub-analysis for the degree of urgency are shown. *p<0.05.

Table 4 Subject preferences

	Enema			
	Predsol	**Pentasa**	**Predfoam**	**Nicotine**
Ease of administration				
1: most preferred	5	6	12	7
2	11	9	1	6
3	3	5	2	7
4: least preferred	5	4	9	4
Ease of retention				
1: most preferred	5	9	13	8
2	5	4	5	7
3	7	6	1	4
4: least preferred	7	5	5	5
Degree of bloating				
1: least bloating	6	6	12	7
2	7	9	2	6
3	5	6	1	7
4: most bloating	6	3	9	4
Overall preference				
1: most preferred	5	4	9	8
2	6	7	5	7
3	6	9	2	5
4: least preferred	7	4	8	4
p Value for overall preference	0.302	0.383	0.629	

p Values quoted for overall preference compare the nicotine enema with each of the others. Some patients graded two enemas as their most preferred. Where this happened their next preference was taken as the three preferred. This accounts for why there are more than 24 in each row. Three way analysis of variance adjusts effectively for this.

of the order of enema administration. This Latin square design has been used in previous crossover studies in which each subject is exposed to a number of similar treatments.[11] We specifically avoided giving each enema for several nights, because a single exposure to each was deemed sufficient to enable patients to identify their preference and also reduced the possibility of change in disease activity over four days only. It should be emphasised that the composite score of disease activity used in this study, based on the UCDAI, has not been independently validated and did not include sigmoidoscopy. Its purpose was to confirm symptomatically active disease at study entry and to permit assessment of factors such as urgency that might affect a patient's ability to retain enemas. A mean activity score of 5.6 in the study confirms the mild to moderate symptomatic activity in these patients. Sigmoidoscopic scoring of disease severity was felt, in this particular instance, to be less relevant to the principal question being addressed—which enema was best retained and tolerated?

Most previous studies of enemas in UC have focused on efficacy—specifically excluded in our study—although some have also briefly considered tolerance and retention. A trial of mesalazine rectal gel compared with a mesalazine foam enema examined ''patient tolerance and acceptability'', as well as the efficacy in patients with mild to moderate left sided colitis.[12] The authors found statistically significant differences between the two enemas in retention, abdominal bloating, and discomfort during administration, with mesalazine gel preferred to the foam; they suggested this was because the gel did not require propellant gas and may have given better adhesion to the mucosa. In a trial that compared 5-ASA foam enemas with 5-ASA liquid enemas for mild to moderate relapses of UC, 81% of patients given the foam had no problems with its use compared with 49% given the liquid ($p<0.01$).[13] Patients found the foam was ''more comfortable, more practical, easier to retain, and interfered less with their evening routine''. A further study that examined hydrocortisone liquid and foam cannot be used for a direct comparison because the foam was first dispensed from a pressurised canister into a syringe before rectal insertion.[14] Hence a greater volume of foam was administered into the rectum, but there was control over its rate of administration. Eight of the 15 patients had difficulty retaining the liquid compared with none of a similar number using the foam ($p<0.01$)—the patients reported a general preference for the foam.

Several factors influence enema retention. The volume determines the degree of rectal stretch and hence the strength of the afferent signal that triggers the urge to defecate; in this study, Predfoam had the advantage of delivering only 50 ml per actuation—significantly lower than the 100 ml of the liquid enemas. The rate of delivery also influences the strength of the defecation reflex—Predfoam is delivered quickly by a burst of propellant gas, whereas the liquid enemas could be administered at a rate chosen by the patient. These two factors may explain patients' polarised views of Predfoam, depending on which had the strongest effect. Viscosity is probably another factor, with more viscous fluids retained more readily—the nicotine enema had a higher viscosity than the other two liquids, Predsol and Pentasa. This greater viscosity was imparted principally by the addition of carbomer to the nicotine enema.[8] A higher viscosity may make administration of a liquid enema more difficult, but in this study there was no significant difference between the three liquid enemas in this respect.

In addition, nicotine has a direct relaxant effect on the smooth muscle of the colon, which could also improve retention. One human in vivo study compared colonic smooth muscle activity in UC patients and healthy volunteers after local perfusion of the colon with solutions of 1.2 mg nicotine or saline.[15] After three minutes, nicotine produced a significant reduction in both muscle tone and activity in both the healthy volunteers ($p = 0.002$) and in UC patients ($p = 0.016$). Two in vitro studies examined strips of circular and longitudinal muscle from patients undergoing bowel resections, and showed that 10 μM nicotine reduced spontaneous tone and activity as well as peak tension after electrical field stimulation.[16 17] This effect was mediated by circular ($p<0.001$) rather than longitudinal muscle ($p = 0.347$) and the presence of nitro-L-arginine methyl ester, an inhibitor of

nitric oxide synthase, abolished the reduction, suggesting that the response is largely mediated by nitric oxide.

In conclusion, there were no significant differences between the nicotine enema and other preparations, in terms of ease of retention and administration, the degree of bloating, and the proportion of patients who achieved complete overnight retention. Nicotine enemas tended to be less well retained overnight in patients with milder urgency, but better retained in those patients with more severe urgency. The polarised reaction of patients to Predfoam, either favouring it most or least, highlights the need for clinicians to review the type of enema used where patients have difficulty with retention, particularly when urgency to defecate is a problem—several of our study patients already taking a particular type of enema, either a foam or liquid, found the other type easier to retain on direct comparison.

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